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Application of: Schneider *et al.* Confirmation No.: 1583

Application No.: 09/305,084 Group Art Unit: 1643

Filed: May 4, 1999 Examiner: Canella, Karen A.

For: Cancer Treatment with Endothelin Receptor Antagonists Attorney Docket No.: 5914-080-999

DECLARATION OF DR. ROBERT J. SCHNEIDER AND DR. SUMAYAH JAMAL UNDER 37 C.F.R. 1.131

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

We, ROBERT J. SCHNEIDER and SUMAYAH JAMAL, hereby state and declare as follows:

1. I, Robert J. Schneider, am a citizen of the United States, and currently a Professor of Microbiology at New York University.

2. I, Sumayah Jamal, am a citizen of the United States, and currently an Assistant Professor of Dermatology at New York University.

3. We are co-inventors of the subject matter described and claimed in patent application Serial No. 09/305,084, entitled, "Cancer Treatment with Endothelin Receptor Antagonists" (the "'084 application"). New York University is the assignee of the '084 application.

4. Attached as Exhibit A is a copy of claims 43 to 59, which we understand will be pending on entry of an Amendment being submitted with this Declaration. The invention claimed relates to the treatment of melanoma by selectively antagonizing the endothelin B

receptor. Antagonists that can be used include peptide inhibitors, antibodies, and compounds that selectively antagonize the endothelin B receptor, such as BQ788, IRL-1038, and RES-701-1.

5. Attached hereto are Exhibit B1, a copy of a two page document entitled "Postdoctoral research proposal: Growth Regulation of the Melanocyte" written by Dr. Jamal, and Exhibit B2, copies of front and back of five sequential pages from the notebook of Dr. Jamal entitled "Book II" (the back of the first notebook page copied for Exhibit B2 did not bear any writing and is thus not included in the Exhibit, providing a total of nine pages in Exhibit B2). Although the dates of Exhibits B1 and B2 have been redacted in accordance with standard practice, all are prior to December 22, 1998.

6. Attached hereto are Exhibit C1, a copy of a page from the notebook of Dr. Jamal entitled "Book II" bearing page number 088; Exhibit C2, copies of front and back of two sequential pages from the notebook of Dr. Jamal entitled "Book III" (the back of the second notebook page copied for the Exhibit did not bear any writing and is thus not included, providing a total of three pages in Exhibit C2); Exhibit C3, copies of four sequential pages from the notebook of Dr. Jamal entitled "Book III"; Exhibit C4, copies of two sequential notebook pages from the notebook of Dr. Jamal entitled "Book III," each bearing page number 43; and Exhibit C5, copies of two sequential notebook pages from the notebook of Dr. Jamal entitled "Book III," each bearing page number 58. Although the dates of Exhibits C1 to C5 have been redacted according to standard practice, the dates range from just prior to December 22, 1998 to prior to the date of filing the above-captioned application, May 4, 1999.

7. As shown by Exhibits B1 and B2, prior to December 22, 1998, we conceived of antagonizing the endothelin B receptor for the treatment of melanoma, and demonstrated the use of antagonists, such as BQ788, for this purpose. In particular, prior to December 22,

1998, we recognized that loss of E-cadherin function in melanoma correlated with tumor invasiveness, and sought ways in which to up-regulate or restore expression of E-cadherin as a therapeutic intervention. We identified the endothelin-1 receptors as candidate targets for antagonism, based on our hypothesis that antagonism of the endothelin receptors would prevent down regulation and/or increase expression of E cadherin in melanoma cells. Prior to December 22, 1998, we conducted experiments with various inhibitors of the endothelin receptors and identified the endothelin B receptor as the one responsible for regulating expression of E cadherin. Our experiments showed that selective antagonists of the endothelin B receptor, such as BQ788, restored E cadherin expression in melanoma cells in a physiologically relevant setting, whereas inhibitors of the endothelin A receptor did not demonstrate this effect. Thereafter, as shown by Exhibits C1 and C2, we pursued experiments to elucidate the role of the endothelin B receptor in the regulation of E-cadherin expression in melanoma, which are reflected in the '084 application filed May 4, 1999.

8. As shown in Exhibit B1, prior to December 22, 1998, we recognized that the adhesion molecule E-cadherin was of primary importance to the maintenance of the normal cell-cell contacts between melanocytes and keratinocytes, and that loss of E-cadherin expression in melanocytes is associated with tumor invasiveness and, thus, a key step in the development of melanoma. Exhibit B1 further demonstrates that prior to December 22, 1998 we proposed both that E-cadherin function in maintaining cell-cell contacts was dependent on the endothelin receptor pathway, and that modulation of this pathway would reverse the invasive metastatic phenotype of melanoma cells.

9. Exhibit B2 shows the protocol, results and conclusions of an experiment entitled "6d ET-1 Stimulation of 20'FM2030" by Dr. Jamal. As indicated on pages 5 and 6 of the Exhibit, page 5 is labeled "Results," Exhibit B2 demonstrates that prior to December 22, 1998 we recognized that stimulation of melanoma cells with endothelin (ET-1) decreases

expression of E-cadherin and increases mobility of β-catenin, and that these effects are blocked by administration of an endothelin B receptor antagonist, BQ788, but not by administration of an endothelin A receptor antagonist, BQ 123 (indicated as 788 and 123, respectively, on page 5 of the Exhibit). Therefore, we concluded prior to December 22, 1998, memorialized on page 8 of Exhibit B1, that the effects of endothelin stimulation on the melanoma cells was mediated by the endothelin B receptor (abbreviated ETRB on page 8 of the Exhibit).

10. Exhibits C1 to C5, each represent experiments performed by Dr. Jamal. The Exhibits demonstrate that after recognition that E-cadherin expression was modulated by the endothelin B receptor response to endothelin, we embarked on studies to further characterize the pathway through which E-cadherin was regulated. Exhibit C1 describes the experiment "2d ET Stim of SKMEL 28 +/- Caspase 8 Inhibitor." Exhibit C1 demonstrates that we recognized the endothelin response of melanoma cells was associated with caspase activity and that we were investigating the relationship between the expression of β-catenin and caspase 8 activity. Exhibit C2 describes the protocol and results of the experiment, "2d ET Stim of SKMEL28 with Titration of IETD" (IETD is a caspase 8 specific inhibitor). Page 2, "Addendum," of Exhibit C2 demonstrates that we were continuing to pursue the regulation to E-cadherin by endothelin-1, in particular the dependence of β-catenin and $p120^{CTN}$ (abbreviated as p120 on page 2) levels and integrity on caspase 8 activity. Exhibit C3 describes the protocol and results of the experiment, "2D ET STIM of SKMEL28 – Inhib. Titration." The Exhibit demonstrates that the effect of caspase inhibitors IEDT, DEVD, VETD, YVAD, and LEHD on the endothelin-1 stimulation of melanoma cells was being investigated. Page 4 of exhibit C3, "Concl," demonstrates that we had determined that caspase 1, 4, 5, and 9 were unlikely to be involved in the endothelin-1 stimulated downregulation of E-cadherin. Exhibit C4 presents the protocol and results of the

experiment, "2d ET Stim of SKMEL28 to look at Cas 8 activation." The shows that we were pursuing endothelin-1 activation of caspase 8. Exhibit C5 shows the results of an experiment of stimulation of FM1054 cells with endothelin-1. The conclusions demonstrate an appreciation of the correlation between the time course of E-cadherin and β-catenin down regulation and caspase 8 activation. The conclusions further note the increase in $p120^{CTN}$ mobility over the course of the experiment.

11. On May 4, 1999 we filed the above-captioned application.

12. In conclusion, as shown by Exhibits B and C, we conceived of and reduced to practice a method for therapeutic intervention in melanoma by antagonizing the endothelin B receptor as claimed in the '084 application prior to December 22,1998, and/or conceived of the method prior to December 22,1998 and diligently reduced it to practice thereafter.

13. We declare further that all statements made in this Declaration of our own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

7/24/06
DATE

Robert J. Schneider

7/24/06
DATE

Sumayah Jamal